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Platinum Priority – Benign Prostatic Hyperplasia – Editor's Choice

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Randomised Clinical Trial of Prostatic Artery Embolisation Versus a Sham Procedure for Benign Prostatic Hyperplasia

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Abstract

Background: Prostatic artery embolisation (PAE) has been associated with an improvement of lower urinary tract symptoms associated with benign prostatic hyperplasia (LUTS/BPH), but conclusive evidence of efficacy from randomised controlled clinical trials has been lacking.
Objective: To assess the safety and efficacy of PAE compared with a sham procedure in the treatment of LUTS/BPH.
Design, setting, and participants: A randomised, single-blind, sham-controlled superiority clinical trial was conducted in 80 males ≥45 yr with severe LUTS/BPH refractory to medical treatment from 2014 to 2019 in a private clinic, with efficacy assessments at 6 and 12 mo after randomisation. One patient in the PAE group and three in the sham group did not complete the study.
Intervention: Patients were randomised 1:1 upon successful catheterisation of a prostatic artery to either PAE or a sham PAE procedure without embolisation. After 6 mo, all 38 patients randomised to the sham group who completed the single-blind period underwent PAE, and both groups completed a 6-mo open period.
Outcome measurements and statistical analysis: An intention-to-treat analysis of all randomised patients was performed. The coprimary outcomes were the change from baseline to 6 mo in the International Prostate Symptom Score (IPSS) and the quality of life (QoL) score at 6 mo, analysed with analysis of covariance and *t* test, respectively.
Results and limitations: Mean age was 63.8 ± 6.0 yr, baseline IPSS 26.4 ± 3.87, and QoL score 4.43 ± 0.52. At 6 mo, patients in the PAE arm had a greater improvement in IPSS, with a difference in the change from baseline of 13.2 (95% confidence interval [CI] 10.2–16.2, $p < 0.0001$), and a better QoL score at 6 mo (difference: 2.13; 95% CI 1.57–2.68, $p < 0.0001$) than the patients in the sham arm. The improvements in IPSS and QoL in the sham group 6 mo after they performed PAE were, respectively, 13.6 ± 9.19 ($p < 0.0001$) and 2.05 ± 1.71 ($p < 0.0001$). Adverse events occurred in 14 (35.0%) patients after PAE and in 13 (32.5%) after sham, with one serious adverse event in the sham group during the open period. No treatment failures occurred. Limitations include a single-centre trial, only severe LUTS/BPH, and follow-up limited to 12 mo.
Conclusions: The improvements in subjective and objective variables after PAE are far superior from those due to the placebo effect.
Patient summary: Clearly superior efficacy of prostatic artery embolisation (PAE) compared with a sham procedure was found in this study, which supports the use of PAE in patients with typical symptoms associated with benign prostatic hyperplasia.

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1. Introduction

Benign prostatic hyperplasia (BPH), a condition often associated with lower urinary tract symptoms (LUTS), has a prevalence rate of over 50% in men over 60 yr old, which increases with age [1,2]. Medication such as alpha-blockers, 5-alphareductase inhibitors (5-ARIs), or both are usually the first-line approach [3–6]. Other treatment options include minimally invasive treatments, such as prostatic urethral lift and water vapour thermal therapy [7–13]. Prostatectomy is the gold standard and may be transurethral (transurethral resection of the prostate [TURP]), if the prostate is smaller than 80 cm^3, or by open surgery for larger prostates. Laser enucleation, transurethral vaporisation of the prostate, and photoselective vaporisation of the prostate may allow endoscopic treatment when the prostate is larger than 80 cm^3 [9,8–13].

Prostatic artery embolisation (PAE) is a minimally invasive treatment that has been shown in many observational studies and meta-analyses to be safe and effective, reducing LUTS/BPH [14–22]. In addition, many phase II trials without controls already exist, showing the safety and efficacy of PAE for BPH. However, LUTS/BPH is known to be very susceptible to placebo treatments, and conclusive demonstration of efficacy will require randomised controlled trials, but until now only three randomised clinical trials of PAE have been published, all comparative to TURP and none has conclusively demonstrated the efficacy of PAE in LUTS/BPH: a study in 107 patients did not find statistically significant differences between TURP and PAE at 12 and 24 mo in clinical and functional outcomes except for a greater decrease in prostate volume (PV) in the TURP group [23]; another study in 30 patients has shown a greater effect of TURP at 12 mo in the International Prostate Symptom Score (IPSS) and quality of life (QoL) scores and in objective outcomes, but the trial design did not allow a proof of PAE efficacy [24]; and a noninferiority trial of PAE to TURP in 99 patients has shown superiority of TURP in secondary outcomes at 3 mo (PV, maximum urine flow rate [Qmax], and postvoid residual urine volume [PVR]), but was inconclusive regarding noninferiority in clinical outcomes [25]. Therefore, PAE is still at the investigational phase, as evidence of efficacy compared with standard treatment has not yet been clearly demonstrated and randomised placebo-controlled clinical trials have not previously been conducted. The aim of this study was to assess the safety and effect of PAE above and beyond the placebo effect versus those of a sham procedure for the treatment of patients with severe LUTS/BPH not adequately controlled by medical therapy with alpha-blockers.

2. Patients and methods

2.1. Study design

A single-centre, parallel-group, single-blind, randomised clinical trial was conducted to test the superiority of PAE versus a sham PAE procedure, consisting of a single-blind phase with the primary efficacy analysis 6 mo after randomisation, followed by an open extension phase where the patients of the sham trial arm crossed over to the PAE arm and a final evaluation was done 12 mo after randomisation.

The study was conducted at Hôpital Saint Louis in Lisbon, Portugal; the study protocol was approved by the in-house Research Ethics Committee (approval numbers 7-2013/09/24 [initial protocol] and 12-2016/04/21 [protocol amendment]), and all patients gave written informed consent.

2.2. Patients

The inclusion criteria were as follows: males over 45 yr old; diagnosis of LUTS/BPH based on clinical history, digital rectal examination, urinalysis, transrectal ultrasound (TRUS), and prostate-specific antigen (PSA); severe LUTS defined, in a screening and in a baseline visit 2 wk apart, by an IPSS of $\geq$20 and a QoL score of $\geq$3 after a minimum of 6-mo treatment with alpha-blockers for LUTS/BPH; Qmax $<$12 ml/s; PV $\geq$ 40 cm^3; accepting the risk of developing sexual dysfunction after treatment; and successful catheterisation of one of the prostatic arteries (technical success). The exclusion criteria were the following: computed tomography (CT) angiography showing that prostatic arteries were not feasible for PAE; previous surgical or invasive prostate treatments such as TURP, transurethral microwave therapy, transurethral needle ablation, laser, or any other minimally invasive treatment; acute or chronic prostatitis or suspected prostatitis including chronic pain, intermittent pain, or abnormal sensation in the penis, testis, anal, or pelvic area in the previous 12 mo; history of prostate or bladder cancer or pelvic irradiation; active or recurrent urinary tract infections (more than one episode in the previous 12 mo); history of neurogenic bladder or LUTS secondary to neurologic disease; advanced atherosclerosis and tortuosity of iliac and prostatic arteries; secondary renal insufficiency (due to prostatic obstruction); large bladder diverticula or stones; detrusor failure; previous history of acute urinary retention; current severe, significant, or uncontrolled disease; bleeding disorder such as haemophilia, clotting factor deficiency, anticoagulation, or bleeding diathesis; hypersensitivity or contraindication to tamsulosin use; mental condition or disorder that would interfere with the patient's ability to provide informed consent; participation in a study of any investigational drug or device in the previous 3 mo; and administration of the 5-ARIs finasteride and dutasteride in the previous 6 and 3 mo, respectively. The latter criterion was changed by a protocol amendment to the administration of the 5-ARIs finasteride and dutasteride in the previous 2 wk and 4 mo, respectively (these patients may be included if they stop those medications and replace them for tamsulosin, alfuzosin, or silodosin for at least 2 wk and 4 mo, respectively).

2.3. Procedures

The patients were evaluated in a screening visit. After signing the informed consent, urinalysis, uroculture, serum creatinine, bladder ultrasonography, TRUS, and pelvic magnetic resonance imaging (MRI) to assess PV were

performed, and study variables were collected. All medication was stopped and the patients were re-evaluated 2 wk later for eligibility in a baseline visit. In cases of suspected prostate cancer, 12-core prostate biopsy was performed. If the patient remained eligible, the following medications were prescribed and continued for 7d: omeprazole 20 mg once daily, and naproxen 1000 mg and ciprofloxacin 500 mg twice a day. For ethical reasons, tamsulosin 0.4 mg once daily was administered until LUTS were controlled. A protocol amendment allowed the prescription of alfuzosin or silodosin in order to comply with patient preferences, but in the end, all patients were prescribed tamsulosin. The decision to stop tamsulosin was made by the study physician, who evaluated the patient by phone calls on days 1, 7, and 14 after PAE, and in clinic visits at months 1, 3, and 6, and was based on a reduction of the IPSS by more than three points and the QoL score by more than one point. PAE was scheduled to the following 2 d, and the patients were admitted to the hospital 2 h before and discharged 3–5 h after the procedure.

The medication during the procedure, catheterisation of the prostatic arteries, and embolisation have been described elsewhere [17,19,26] and are detailed in the Supplementary material. After identifying the left prostatic arteries, a road map was obtained with the catheter at the origin of the artery from which these arteries originate. If this examination confirmed that the anatomy of prostatic arteries shown by angio-CT and catheterisation of at least one prostatic artery was possible, the patient was then randomised to the PAE group or the sham procedure group in a 1:1 ratio. A randomisation list consisting of permuted blocks of size varying between 4 and 8 was prepared by the trial biostatistician (A.G.O.), and the allocation sequence was concealed using opaque envelopes numbered sequentially. Patients were blinded to the intervention received until the end of single-blind period.

In the PAE group, Bead Block (BTG plc, London, UK) 300–500 μm was used; in the sham group, after catheterisation of one prostatic artery, the catheter was removed and no particles were injected, but there was a wait of some minutes before the removal of the catheter in order to avoid revealing the treatment arm to patients of the sham group. All procedures were performed by five interventional radiologists with 10 yr (J.M.P. and T.B.), 5 yr (N.V.C.), and 3 yr (D.T. and J.P.) of experience in PAE.

Thereafter, the patients were evaluated in clinic visits at months 1, 3, and 6. At month 1, PV and degree of ischaemia were evaluated by pelvic MRI. Medications that might interfere with the evaluation of efficacy variables, such as psychotherapy, medications prescribed for overactive bladder, male hormonal replacement, and medication that could induce urinary retention and known to interact with tamsulosin, were not allowed. A full account of the forbidden medication is presented in the Supplementary material. Adverse events (AEs) were recorded at each study visit and graded according to the Clavien-Dindo classification.

At month 6, after the final visit of the single-blind study period, the patients entered a 6-mo open extension period. The patients who had been randomised to the sham group were then submitted to PAE with exactly the same procedure and were evaluated by the same methods at 7, 9, and 12 mo after randomisation. The patients randomised to PAE continued under observation and had a final study visit at month 12.

2.4. Outcomes

The coprimary efficacy variables were the change from baseline to 6 months in the IPSS and the QoL score at 6 mo. The secondary outcomes were the BPH Impact Index, the 15-item International Index of Erectile Function (IIEF-15), PV assessed with TRUS, Qmax, PVR, and PSA. Procedure variables were procedure and fluoroscopy times, radiation dose, and pain measured with a visual analogue scale from 0 (no pain) to 10 (worst pain) during the procedure, at discharge, and the next morning.

2.5. Statistical analysis

For sample size calculations, the standard deviation of the change from baseline of the IPSS in a previous prospective study of 300 PAE was 7.4. With 40 patients per study group, the clinical trial would be powered to 85% to show, at the two-sided 0.05 level, a difference of five points in change of the IPSS from baseline between groups. This difference has been reported to correspond to the perception of a slight to moderate improvement in IPSS by LUTS/BPH patients [27].

Data analysis was performed by the intention-to-treat principle for all randomised patients. The main analysis was between-group comparison of the coprimary outcomes at month 6. In patients who did not complete the trial, missing data were imputed by the last observation carried forward. The between-group difference in the change from baseline in the IPSS was tested at the two-sided 5% level, with analysis of covariance with the baseline IPSS as a covariate. The between-group difference in the mean QoL score at month 6, the coprimary efficacy variable, was compared with the Student's t test. In order to control the overall alpha error at the 5% significance level, a serial gatekeeper procedure was adopted [28]: the primary efficacy variable would be tested at the 5% significance level, and if the null hypothesis was rejected, then the coprimary efficacy variable would be tested also at the 5% significance level; otherwise, no further significance tests would be performed. If both tests were significant, the study would conclude for a statistical difference in both primary efficacy variables at the nominal p value.

Between-group comparisons of the change from baseline in each secondary efficacy variable were also performed with analysis of covariance, with the p values and 95% confidence intervals (CIs) corrected for multiple comparisons with the Bonferroni procedure. To control for the administration of tamsulosin during the trial, generalised estimation equations with robust variance estimates and the assumption of an unstructured correlation structure were used for between-group comparison of each efficacy variable over time, adjusting for the number of days

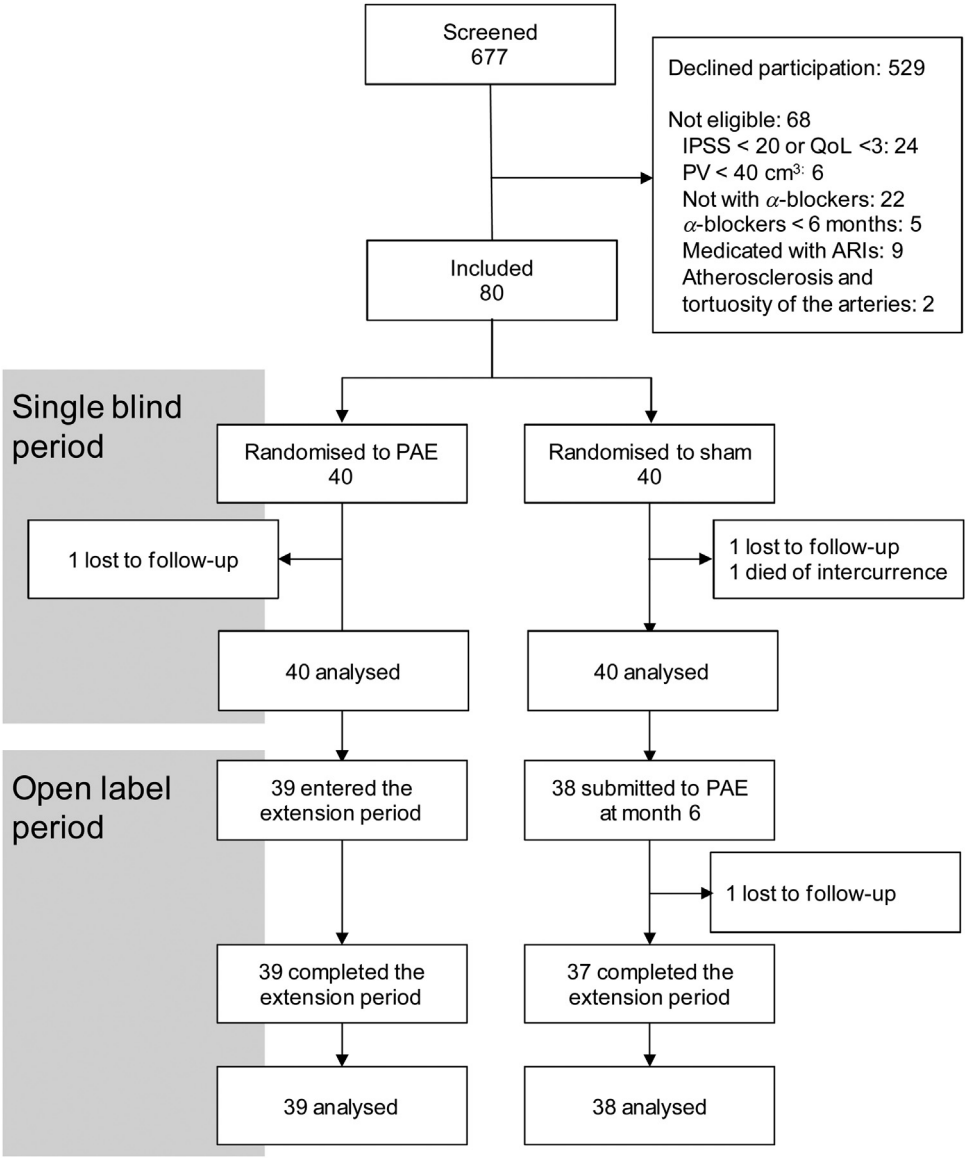

Fig. 1 – CONSORT diagram. ARI = alphareductase inhibitor; IPSS = International Prostate Symptom Score; PAE = prostatic artery embolisation; PV = prostate volume; QoL = quality of life.

without tamsulosin medication at each time point. Differences between groups in efficacy variables at 12 mo were tested with the Student's *t* test. Evidence of statistical significance was considered when *p* values were < 0.05. Stata 15 (Stata Corp., College Station, TX, USA) was used for all analyses.

3. Results

From 2 September 2014 to 3 March 2018, 80 patients with severe LUTS/BPH refractory to medical therapy with alpha blockers for at least 6 mo were enrolled into the study. Forty patients were randomised to each trial arm. No patient was excluded due to difficult vascular situations during the catheterisation. In the trial single-blind period, one patient in each group was lost to follow-up after months 1 and 3. One patient of the sham group died after month 1 from acute cholecystitis with sepsis, which was considered not related to the procedure. In the open extension period, one patient from the sham group dropped out from the study after month 7 (Fig. 1). No patient was prematurely discontinued because of clinical failure or complications of the disease. There were no protocol deviations due to missing study visits, administration of forbidden medication, or other reasons.

The study population had a mean age of 63.8 ± 6.0 yr (range 48–76 yr), a baseline IPSS of 26.4 ± 3.87 (range 20–33), a QoL score of 4.43 ± 0.52 (range 3–5), PV by TRUS of 79.5 ± 39.1 cm^3 (range 40–235 cm^3) and by MRI of 81.6 ± 41.2 cm^3 (range 30–260 cm^3), and a Qmax of

Table 1 – Baseline patient characteristics.

Variable	Sham group		PAE group	
	Median	Q1–Q3	Median	Q1–Q3
Patient data				
Age (yr)	64	60–68.5	64	59.0–67.5
BMI (kg/m^2)	26.9	25.5–27.9	26.1	24.5–29.8
Creatinine serum (mg/dl)	0.87	0.70–0.96	0.88	0.77–0.96
Outcome variables				
IPSS	27.5	24.0–30.5	25.5	22.5–29.0
QoL	4.5	4.0–5.0	4.0	4.0–5.0
BPH-II	10.0	8.5–11.0	10.0	8.0–11.5
PSA (ng/dl)	3.10	1.59–3.71	3.04	1.54–5.15
Qmax (ml/s)	7.30	4.90–9.40	7.90	5.55–10.2
PVR (ml)	106	60–178	119	72–155
PV (TRUS), cm^3	66.0	55.5–94.5	63.5	55.5–100.0
PV (MRI), cm^3	66.5	50.0–101.5	68.5	58.0–103.5
IIEF-15	46.0	22.0–52.5	52.5	40.0–61.0
Procedure data				
Procedure time (min)	30	30–45	75	60–90
Fluoroscopy time (min)	2.0	1.0–5.7	15.0	12.0–24.8
Radiation dose (Gy.cm^2)	102.8	60.5–135.2	201.5	130.0–335.6

BMI = body mass index; BPH-II = Benign Prostate Hyperplasia Impact Index; IIEF-15 = 15-item International Index of Erectile Function; IPSS = International Prostate Symptom Score; MRI = magnetic resonance imaging; PAE = prostatic artery embolisation; PSA = prostate-specific antigen; PV = prostate volume; PVR = postvoid residual urine volume; Q1 = first quartile; Q3 = third quartile; Qmax = maximum urinary flow rate; QoL = quality of life; TRUS = transrectal ultrasonography.

7.39 ± 2.74 ml/s. The study groups were similar regarding the baseline characteristics (Table 1). PAE was bilateral in all but three (7.5%) patients.

The change over time in the two study periods is shown in Figure 2 for the subjective outcomes and in Figure 3 for the functional outcomes. The decrease from baseline to month 6 in IPSS was 5.03 ± 8.13 in the sham group and 17.1 ± 7.25 in the PAE group (difference between groups of changes from baseline: 13.2, 95% CI 10.2–16.2, $p < 0.0001$). At month 6, the mean IPSSs were 21.9 ± 7.34 in the sham

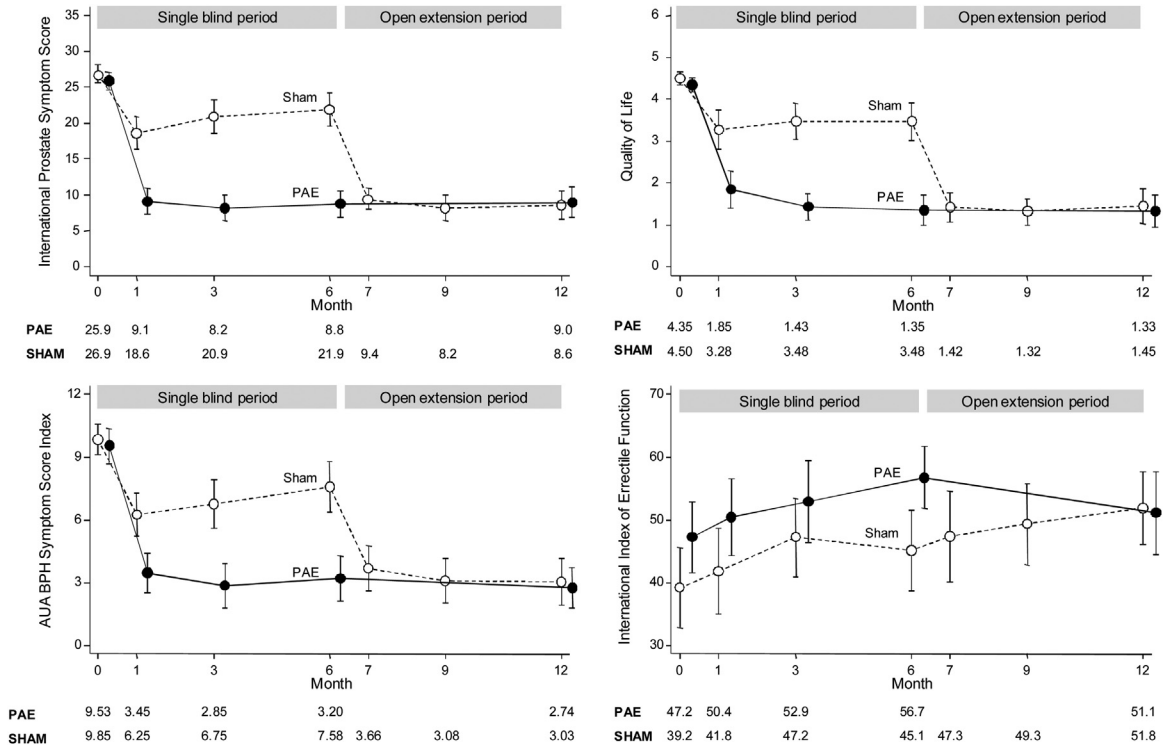

Fig. 2 – Mean values over time after prostatic artery embolisation and a sham procedure in the subjective outcomes in the two study periods. In the second period, patients in the sham group were submitted to PAE. Solid circles represent the PAE group, open circles represent the sham group, and error bars represent 95% confidence intervals. The numbers are the mean values observed at each study visit. AUA = American Urological Association; BPH = benign prostatic hyperplasia; PAE = prostatic artery embolisation.

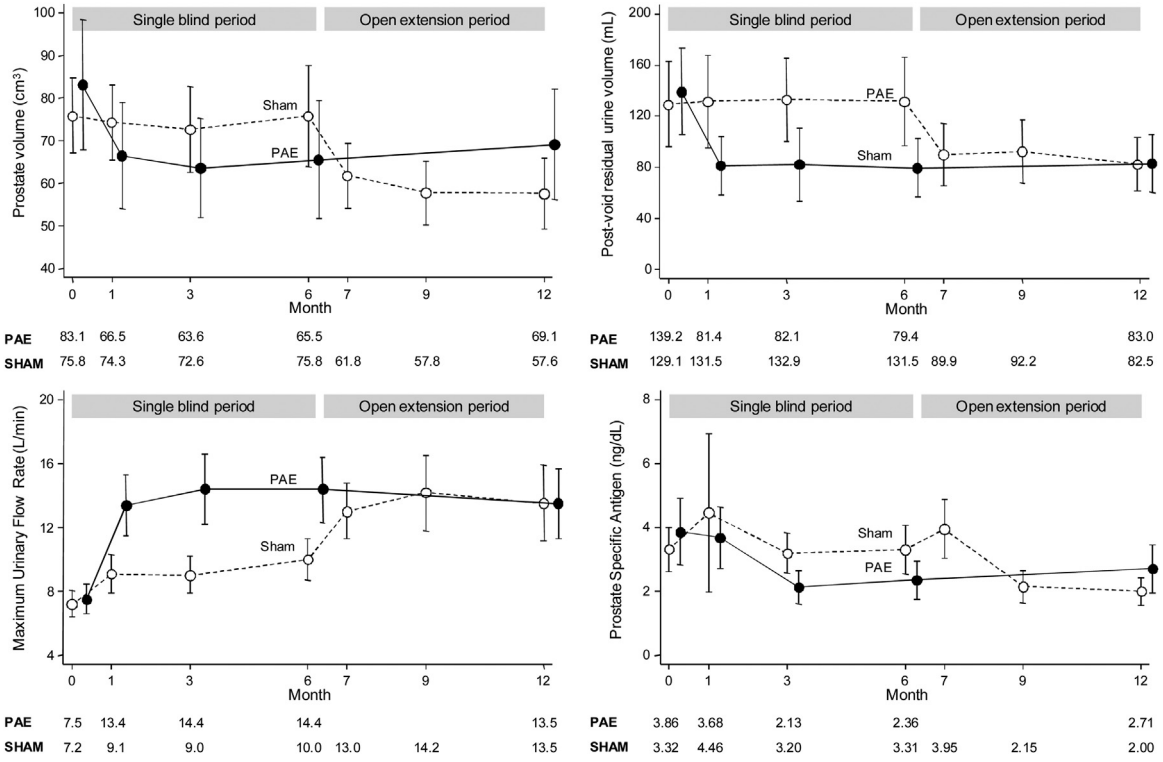

Fig. 3 – Mean values over time after prostatic artery embolisation and a sham procedure in the functional outcomes in the two study periods. In the second period, patients in the sham group were submitted to PAE. Solid circles represent the PAE group, open circles represent the sham group, and error bars represent 95% confidence intervals. The numbers are the mean values observed at each study visit. PAE = prostatic artery embolisation.

group and 8.75 ± 5.76 in the PAE group. The mean QoL scores at month 6 were 3.48 ± 1.38 and 1.35 ± 1.12 in the sham and PAE groups (difference in the means of QoL scores between groups at month 6: 2.13, 95% CI 1.57–2.68, $p < 0.0001$), respectively, corresponding to decreases from baseline of 1.03 ± 1.19 and 3.00 ± 1.13, respectively (-$p < 0.0001$).

In the secondary efficacy variables, there was greater improvement, both statistically and clinically significant, in Benign Prostate Hyperplasia Impact Index score and in all functional outcomes. There was no evidence of worsening of the IIEF-15 score. In the PAE group, between baseline and 12 mo, the mean Qmax increase was 5.96 ml/s (95% CI 3.95–7.97 ml/s, $p < 0.0001$), while between months 6 and 12, there was no statistically significant change (95% CI −2.49 to 0.49 ml/s, $p = 0.18$). Table 2 presents the results for all efficacy variables. In the sham group, 34 (91.9%) patients were still taking tamsulosin at the end of the main study, compared with only two (5.13%) in the PAE group ($p < 0.0001$). The average number of days under tamsulosin medication was 184 ± 38 in the sham group and 38 ± 52 in the PAE group ($p < 0.0001$). Controlling of the between-group comparison by the administration of tamsulosin did not change the results: the average between-group differences at each time point throughout the study period were 9.56 (95% CI 6.79–12.3, $p < 0.001$) in the IPSS and 1.33 (95% CI 0.75–1.91, $p < 0.001$) in the QoL score.

PAE was performed in all 38 patients of the sham group who completed the single-blind phase. Procedure data were not significantly different from those of patients in the PAE group (procedure time 71.3 ± 18.1 min, fluoroscopy time 19.4 ± 9.71 min, radiation dose 247.9 ± 153.8 Gy.cm^2). There was a statistically significant improvement at the 12-mo evaluation in all efficacy variables except for IIEF-15. In the comparison with the results at 12 mo in the PAE group, there were no statistically significant differences in any efficacy variables (unadjusted p values). The 95% CI values of the between-group difference at 12 mo were 2.3–3.53 ($p = 0.66$) in the IPSS and 0.48–0.63 ($p = 0.80$) in the QoL score.

No patient in the sham group mentioned pain during PAE, at discharge, or next morning. In the PAE group, no patient complained of pain during the procedure, two complained of pain at discharge, and two complained the next morning. All patients were discharged between 2 and 6 h after PAE.

There were 16 AEs in 14 (35.0%) patients in the PAE group and 17 in 13 (32.5%) patients in the sham group. In the 38 patients of this group who underwent PAE, there were 13 AEs in 11 (28.9%) patients (Table 3). Among the 29 AEs in the 78 patients who were submitted to PAE, 25 (86.2%) were of grade I, three (10.3%) of grade II, and one (3.4%) of grade IIIa, consisting of expelled small prostate fragments causing haematuria and acute urinary retention, treated by TURP and followed by complete recovery without sequelae. Two patients with dysuria and burning urethral pain, and one

Table 2 – Change from baseline to month 6 after a sham procedure and PAE.

Variable	Sham		PAE		Difference PAE – sham				*p* value
	Mean	SD	Mean	SD	Mean	SD	95% CI		
IPSS	−5.03	8.13	−17.1	7.25	−13.2	1.50	−16.2	−10.2	<0.0001
QoL	−1.03	1.19	−3.00	1.13	−1.99	0.26	−2.51	−1.46	<0.0001
BPH-II	−2.28	3.69	−6.33	4.09	−4.28	0.78	−6.49	−2.08	<0.0001[a]
PSA (ng/dl)	−0.02	2.13	−1.51	2.17	−1.22	0.37	−2.27	−0.17	0.01[a]
Qmax (ml/s)	2.80	4.75	6.82	6.25	4.22	1.19	0.86	7.58	0.005[a]
PVR (ml)	8.63	127.1	−59.9	109.3	−60.6	19.9	−116.7	−4.6	0.03[a]
PV (cm^3)	−0.06	20.9	−17.6	18.5	−16.8	4.38	−29.2	−4.52	0.002[a]
IIEF-15	5.95	18.7	9.53	15.4	7.28	3.41	−2.32	16.9	0.29[a]

BPH-II = Benign Prostate Hyperplasia Impact Index, a four-item self-administered questionnaire measuring how LUTS affect four key domains (physical discomfort, worry about health, bother, and impact on usual activities) scored from 0 to 13 points, with lower scores indicating less important symptoms; CI = confidence interval; IIEF-15 = International Index of Erectile Function, a 15-item self-administered questionnaire with a total score from 0 to 75, with lower values indicating more severe erectile dysfunction, which evaluates the four main domains of male sexual function (erectile function, orgasmic function, sexual desire; and intercourse satisfaction); IPSS = International Prostate Symptom Score, a seven-item self-administered questionnaire with a total score ranging from 0 to 35, higher scores indicating more severe LUTS; LUTS = lower urinary tract symptoms; PAE = prostatic artery embolisation; PSA = prostate-specific antigen; PV = prostate volume by transrectal ultrasonography; PVR = postvoid residual urine volume; Qmax = maximum urinary flow rate; QoL = the eighth question in the IPSS measuring disease-specific quality of life from 0 to 6, with higher scores indicating worse quality of life; SD = standard deviation.
[a] *p* values and 95% confidence intervals adjusted for multiple comparisons.

Table 3 – Adverse events.

Adverse event	After sham	After PAE		
	(*n* = 40)	PAE group (*n* = 40)	Sham group (*n* = 38)	Total (*n* = 78)
Number with adverse event	13 (32.5)	14 (35.0)	11 (28.9)	25 (32.1)
Burning perineal pain		1 (2.5)		1 (1.3)
Burning urethral pain	2 (5.0)	2 (5.0)	1 (2.6)	3 (3.8)
Dysuria	2 (5.0)	1 (2.5)	2 (5.3)	3 (3.8)
Ecchymosis	9 (22.5)	2 (5.0)		2 (2.6)
Haematospermia		3 (7.5)	4 (10.5)	7 (9.0)
Haematuria	2 (5.0)	3 (7.5)	2 (5.3)	5 (6.4)
Inguinal haematoma		3 (7.5)	1 (2.6)	4 (5.1)
Prostate fragment expelled			1 (2.6)	1 (1.3)
Rectorrhagia	2 (5.0)		2 (5.3)	2 (2.6)
Urinary tract infection		1 (2.5)		1 (1.3)

PAE = prostatic artery embolisation.

patient with urinary tract infection required medical treatment; all other AEs subsided spontaneously. Detailed tables of efficacy variables and AEs are presented in the Supplementary material.

4. Discussion

The single-blind period of this randomised clinical trial fills the gap in the evidence base on the treatment effect of PAE by demonstrating both clinically and statistically significant differences in patients treated with PAE as compared with patients submitted to a sham procedure. In addition, the trial open extension period offers evidence of sustainability of effects up to 12 mo.

PAE is considered experimental in the urology guidelines [11,12]. For a novel technique such as PAE to be considered as a first-line option, sham-controlled trials are very helpful, and hence the present study. Randomised trials with a long-term follow-up comparing PAE and surgery and medical therapy are also important to better understand the role of PAE in the management of patients with LUTS/BPH.

The results of this randomised clinical trial provide clear evidence that the improvement experienced by patients after PAE is due to a real treatment effect that is much larger than the placebo effect associated with the procedure. The marked and sustained amelioration in all primary and secondary outcomes, with no negative influence on erectile function, offers strong evidence that PAE, through the reduction it imposes on prostate size and possibly because of several other mechanisms, actually modifies the course of LUTS/BPH, and this explains the high clinical success rates reported so far with this treatment. The results in this study, which included a 2-wk period for the wash-out of alpha-blockers, are clearly better than the results of the trials where drugs were stopped only after PAE had been performed, and this may explain the different results.

PAE is mostly painless and safe, with most AEs being mild and self-limited. A serious event consisting of expelled

prostate fragments was readily treated with TURP and left no sequels. Others have reported a similar AE in up to 6% of patients after PAE [29–31].

The main limitation of this study was the inclusion of patients with severe LUTS only, as less symptomatic patients may have less pronounced improvement compared with placebo. In addition, the average prostate size of the study participants was rather large (81.6 cm^3), and as larger PVs have been shown by some to correlate with better outcomes after PAE [31], the results from this trial may not be generalisable for prostates smaller than 40 cm^3, which have been reported to show a worse response to PAE [32]. The trial was conducted at a clinical centre with extensive experience in PAE, and with less skilled operators the results may diverge somewhat, although considering the consistency of results of PAE reported by other authors, we would not expect any appreciable difference from our results [17,20–22]. The 6-mo single-blind period is justified because it might not be ethical to withhold treatment for a longer time in patients with severe LUTS refractory to medical treatment and also for fears of patient attrition in the sham group in a long-term trial. We, however, followed up the patients for a further open period of 6 mo during which we have shown no regression of the effects observed after PAE. Moreover, for ethical reasons, randomisation was performed only after confirmation by catheterism that PAE was feasible; otherwise, patients randomised to the sham arm in whom catheterism proved to be unsuccessful would have to be deceived for 6 mo into believing that after the 6-mo open period they would have access to PAE. Technical failures are uncommon because of the preprocedure protocol that we follow, and actually no patient was excluded for that reason.

Major questions still remain regarding the durability of the treatment effect, especially considering a lower impact when compared with surgery on objective parameters such as PV reduction and relief of the bladder outlet obstruction [25]. Noninferiority clinical trials providing data on long-term outcomes after PAE in large patient cohorts are needed to critically assess these issues. Future research should focus on providing comparative studies of PAE with surgery or medical care with appropriate cohort sizes and long-term follow-up. PAE alongside with prostatic urethral lift and water vapour thermal therapy is less invasive than surgery and, thus, might be justified instead of medical treatment, or in patients between medical treatment and surgery on their pathway of care. TURP and other endoscopic treatment options that remove tissue might be the best option in patients who require maximum relief of bladder outlet obstruction. Moreover, further efforts should be made to identify the ideal candidates for PAE. The results of this clinical trial will be a reference for future research consensus panels and guidelines on the management of LUTS/BPH.

5. Conclusions

In conclusion, the improvements in subjective and objective variables after PAE are far superior to those due to the placebo effect, and the results of this single-blind randomised clinical trial clearly establish PAE as a safe and effective minimally invasive treatment for benign prostatic hyperplasia, which, combined with the evidence from randomised clinical trials comparing PAE with TURP, support its role in the treatment of LUTS/BPH. Clinical trials with longer follow-up and noninferiority trials of PAE versus other treatment modalities should be the focus of future research.

***Author contributions*:** Antonio Gouveia Oliveira had full access to all the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis.
Study concept and design: J.M. Pisco, Oliveira.
Acquisition of data: J.M. Pisco, Bilhim, Costa, Torres, J. Pisco.
Analysis and interpretation of data: J.M. Pisco, Oliveira.
Drafting of the manuscript: J.M. Pisco, Oliveira.
Critical revision of the manuscript for important intellectual content: Bilhim.
Statistical analysis: Oliveira.
Obtaining funding: J.M. Pisco.
Administrative, technical, or material support: J.M. Pisco, Pinheiro.
Supervision: J.M. Pisco.
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Appendix A. Supplementary data

Supplementary material related to this article can be found, in the online version, at doi:https://doi.org/10.1016/j.eururo.2019.11.010.

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